Panel Questions for the KAMRA™ Inlay

1. Given the conduct of the studies, including:

    - 777 and 285 protocol deviations in the pivotal and confirmatory trial, respectively, ranging in severity from out-of-window visits to implantation of subjects outside of the enrollment criteria, and
    - Over enrollment into the pivotal trial leading to lack of data poolability between the first 400 and the next 121 subjects

    Do you believe that the data generated represent valid scientific evidence?

2. With regard to pre-specified safety endpoints:

    - The adverse event (AE) target rate of ≤ 5% was not met in the pivotal study nor in the confirmatory study at 12 months

    - The target rate of ≤ 1% per single AE type was not met for several adverse event types in the pivotal and confirmatory studies, in particular:

        » Under the category of secondary surgical intervention (SSI), inlay removal was 3.0% and 6.0% at 12 months, for the pivotal and confirmatory studies, respectively, and the majority of removals were because of visual reasons

    Do you believe the data support the safety of this device for the intended population?

3. Given the following for the pivotal trial cohort:

    - The target of 95% of subjects having a change in manifest refractive spherical equivalent (MRSE) < 1.00 D between two consecutive visits was not met between 30 and 36 months

    - There was a trend toward increasing hyperopia at the later time points

    - The percentage of subjects with > 1.00 D of hyperopic change from baseline reached a maximum of 16.6% at 6 months, and was 10.6% at 36 months

    Do you believe that the applicant has adequately demonstrated that the refractive outcomes following KAMRA implantation are stable at any time point?

4. The applicant proposes the following indication for use (IFU):

   The KAMRA™ Inlay is indicated for the improvement of near vision in presbyopic patients who require near correction. The inlay is intended to be placed intrastromally in the cornea on the visual axis, by way of a femtosecond laser-created pocket using a spot/line separation of 6x6 microns or less. The KAMRA inlay should be placed at a depth equal to or greater than 180 micrometers.

   At 12 months, 80.8 % (399/494) of subjects in the pivotal study had UCNVA of 20/40 or better. However, only 25%, 24%, and 22% of subjects in the pivotal trial, the 6x6 subgroup, and the confirmatory trial, respectively, gained ≥4 lines of UCNVA (= 1 diopter of accommodation) without losing >1 line of letters of UCDVA from baseline at 12 months. Do you believe the data support the proposed IFU of improvement in the near vision?

5. Please discuss the utility of the PRO questionnaire for the claim of subjective improvement in near vision satisfaction without glasses. Please include the following in your discussion:

   - development process
   - question format
   - response options
   - administration process
   - analysis of individual items (not scores)
   - absence of *a priori* hypothesis testing

6. **Note:** The discussion of a Post-Approval Study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered.

If the device is approved, the applicant is proposing an extended follow-up post-approval study (PAS) to continue to follow the patients enrolled in the IDE study for 5 years after device implantation, as well as a new enrollment PAS of 500 patients who will be followed for 3 years after device implantation. Please discuss the following:

a. For the extended follow-up PAS, please discuss whether 5 years post-implantation is an appropriate duration to assess long term device performance.

b. For the new enrollment PAS, please discuss the following:

i. The applicant did not include device explants or distance corrected near visual acuity (DCNVA) in the new enrollment study as study endpoints/parameters to measure device performance. Please discuss the adequacy of the proposed study endpoints/parameters, including the appropriate visual acuity assessments and any other endpoints that should be included.

ii. The applicant did not specify the racial/ethnic subgroups to be included and analyzed in the new enrollment study. In the pivotal study, there is limited data on device performance in African-Americans and Hispanics. Please discuss (i) if subgroup analyses are needed in the new enrollment study to examine device performance among African-Americans and Hispanics, and (ii) if yes, which safety outcomes should be evaluated and if those analyses should be powered.

iii. FDA has identified important postmarket concerns during review of the pivotal study, including the appropriate implantation technique (i.e., depth of cut) and the appropriate management of patients who develop cataracts after the device implantation. Please discuss (i) considerations for assessing these postmarket concerns in the new enrollment study including suggestions on study design, study question/hypotheses, endpoints, and duration, and (ii) any other concerns that need to be evaluated in the postmarket setting.

iv. The applicant is proposing a 3-year follow-up for the new enrollment study which may not be sufficient to evaluate long term outcomes. Please discuss the appropriate duration of follow-up for the new enrollment study in order to assess long term device performance, as well as in light of any other endpoints or postmarket concerns that were raised during panel discussion on the new enrollment study.